General

Guideline Title

American Gastroenterological Association Institute guideline on pharmacological management of irritable bowel syndrome.

Bibliographic Source(s)

Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S, American Gastroenterological Association. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014 Nov;147(5):1146-8. [4 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of evidence (high, moderate, low, very low) and strength of recommendation (strong, weak) are provided at the end of the "Major Recommendations" field.

1. Should linaclotide be used in patients with irritable bowel syndrome with constipation-predominant symptoms (IBS-C)?
   The American Gastroenterological Association (AGA) recommends using linaclotide (over no drug treatment) in patients with IBS-C. (Strong recommendation; High-quality evidence)

   Comments: Patients who place a high value on avoiding diarrhea and avoiding higher out-of-pocket expenses associated with linaclotide may prefer alternate treatments.

2. Should lubiprostone be used in patients with IBS-C?
   The AGA suggests using lubiprostone (over no drug treatment) in patients with IBS-C. (Conditional recommendation; Moderate-quality evidence)

   Comments: Patients who place a high value on avoiding higher out-of-pocket expenses associated with lubiprostone may prefer alternate treatments.

3. Should polyethylene glycol (PEG) laxatives be used in patients with IBS-C?
   The AGA suggests using laxatives (over no drug treatment) in patients with IBS-C. (Conditional recommendation; Low-quality evidence)

4. Should rifaximin be used in patients with IBS with diarrhea-predominant symptoms (IBS-D)?

The AGA suggests using rifaximin (over no drug treatment) in patients with IBS-D. (Conditional recommendation; Moderate-quality evidence)

5. Should alosetron be used in patients with IBS-D?
   The AGA suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms. (Conditional recommendation; Moderate evidence)

6. Should loperamide be used in patients with IBS-D?
   The AGA suggests using loperamide (over no drug treatment) in patients with IBS-D. (Conditional recommendation; Very low-quality evidence)

7. Should tricyclic antidepressants be used in patients with irritable bowel syndrome (IBS)?
   The AGA suggests using tricyclic antidepressants (over no drug treatment) in patients with IBS. (Conditional recommendation; Low-quality evidence)

8. Should selective serotonin reuptake inhibitors be used in patients with IBS?
   The AGA suggests against using selective serotonin reuptake inhibitors for patients with IBS. (Conditional recommendation; Low-quality evidence)

9. Should antispasmodics be used in patients with IBS?
   The AGA suggests using antispasmodics (over no drug treatment) in patients with IBS. (Conditional recommendation; Low-quality evidence)

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Quality of Evidence

Quality Level	Definitions
High	The Committee is very confident that the true effect lies close to that of the estimate of the effect supporting the recommendation
Moderate	The Committee is moderately confident in the estimate of effect supporting the recommendation: the true effect is likely to be close to the estimate of effect, but there is a possibility it will be substantially different
Low	The Committee's confidence in the effect supporting the recommendations is limited: the true effect may be substantially different from the estimate of the effect
Very Low	The Committee has very little confidence in the effect estimate supporting the recommendation: the true effect is likely to be substantially different from the estimate of effect

GRADE Strength of Recommendations

Implications of strong and conditional (weak) guideline recommendations

- Strong recommendations
  - Patients: Most people in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.
  - Clinicians: Most patients should receive the recommended course of action. Adherence to this recommendation according to guidelines could be used as a quality criterion or a performance indicator.
  - Policy makers: The recommendation can be adapted as a policy in most situations.
- Conditional (weak) recommendations
  - Patients: The majority of people in this situation would want the suggested course of action, but many would not. Decision aids are useful in helping patients make decisions consistent with their values and preferences.
  - Clinicians: Examine a summary of the evidence to help patients make a decision that is consistent with their own values and preferences (shared decision making).
  - Policy makers: There is a need for substantial debate and involvement of stakeholders.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Irritable bowel syndrome (IBS)

- IBS with constipation-predominant symptoms (IBS-C)
- IBS with diarrhea-predominant symptoms (IBS-D)

Guideline Category

Management

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To present the official recommendations of the American Gastroenterological Association (AGA) on the use of pharmacological agents for the treatment of irritable bowel syndrome (IBS) in adults

Target Population

Adults with irritable bowel syndrome (IBS)

Interventions and Practices Considered

1. Patients with irritable bowel syndrome with constipation-predominant symptoms (IBS-C)
    - Linaclotide
    - Lubiprostone
    - Polyethylene glycol (PEG) laxatives
2. Patients with IBS with diarrhea-predominant symptoms (IBS-D)

    - Rifaximin
    - Alosetron
    - Loperamide
3. Tricyclic antidepressants
4. Selective serotonin reuptake inhibitors (not recommended)
5. Antispasmodics

Major Outcomes Considered

- Improvement of abdominal pain, constipation, diarrhea and bloating
- Frequency of complete, spontaneous bowel movements
- Rate of side effects of medication, such as idiopathic, non-dose-dependent ischemic colitis, prolongation of the QT interval sedation

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Types of Participants, Interventions, and Comparators

The reviewers included studies of adults (18 years of age and older) with irritable bowel syndrome (IBS) using symptom-based diagnostic criteria. The interventions were linaclotide, lubiprostone, polyethylene glycol (PEG) laxative, rifaximin, alosetron, loperamide, tricyclic antidepressants, selective serotonin reuptake inhibitors, should be noted that there is a lack of comparative effectiveness studies in IBS.

Information Sources and Study Selection

An information specialist, with input from the authors, developed and conducted several literature searches. The following bibliographic databases were searched through the OVID interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and EMBASE. Parallel searches included the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register, and Health Technology Assessment Database. The search strategy comprised controlled vocabulary, including the National Library of Medicine's Medical Subject Headings and keywords. The main search concepts included and combined were "irritable bowel syndrome" and "linaclotide" and "lubiprostone" and "polyethylene glycol" and "rifaximin" and "alosetron" and "tricyclic antidepressants" and "selective serotonin reuptake inhibitors" and "antispasmodics." Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs), meta-analyses, systematic reviews, and health technology assessments. The results were limited to English, human, and 1995 onward (see the "Supplementary Methods" section in the technical review [see the "Availability of Companion Documents" field] for detailed search strategies). An additional search was conducted using the aforementioned Medical Subject Headings and keywords and was limited to meta-analysis and technology assessments from 2004 onward.

In selecting studies, the reviewers followed the umbrella systematic review approach in which the committee identified published systematic reviews that fit predetermined eligibility criteria and were of high methodological rigor. A systematic review was eligible for inclusion if it was recently conducted (search strategy executed within the past 10 years), evaluated the outcomes of interest (outcomes important to patients) outlined in the technical review, and provided a quantitative estimate of effect. The reviewers supplemented this by reviewing additional RCTs not included in the systematic reviews as well as references of relevant articles from the systematic reviews.

The parameters for the first search was between 1/1994-3/2014 and then an additional search was conducted with the parameters of 1/2004-5/2014.

For more information on excluded and included studies and search strategies, refer to the technical review.

Number of Source Documents

136 studies

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Quality of Evidence

Quality Level	Definitions
High	The Committee is very confident that the true effect lies close to that of the estimate of the effect supporting the recommendation
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Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

When systematic reviews were not up to date or were incomplete, the reviewers performed their own meta-analysis (random effects model for 3 or more studies and fixed effects model for 2 studies) using the Cochrane Collaboration's RevMan 5.1 software.

Evaluating the Evidence: Risk of Bias and Study Quality Appraisal

Within the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, randomized controlled trials (RCTs) start as high-quality evidence but can be rated down for 5 possible reasons. Using GRADE, the quality of evidence for each outcome was evaluated for the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. When the systematic reviews did not provide sufficient information to judge the quality of the evidence, individual studies were retrieved. Evidence ratings and qualitative judgments were determined via telephone discussion and consensus. For each question, an overall judgment of quality of evidence was made for a body of evidence that encompassed all critical outcomes.

Synthesis of Results and Summary Measures

When available, quantitative estimates of effect were applied from existing systematic reviews. Additional data were extracted and synthesized for some outcomes using RevMan. If results were incomplete or unclear, study authors or study sponsors were contacted for additional information. Evidence profiles (see Tables 2–10 in the technical review [see the "Availability of Companion Documents" field]) were used to display the summary estimates as well as the body of evidence for each clinical question.

See the technical review for more information on study evaluation.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline was developed by the Clinical Practice and Quality Measures Committee (currently the Clinical Practice Guideline Committee) and approved by the American Gastroenterological Association (AGA) Governing Board.

The guideline was developed using a process outlined in the technical review (see the "Availability of Companion Documents" field). Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and best practices as outlined by the Institute of Medicine. GRADE methodology was used to prepare the background information for the guideline and the technical review that accompanies it (see the "Rating Scheme for the Strength of the Recommendations" field). Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review.

Members of the guideline panel, along with AGA support staff and a patient/consumer representative, met in person with the authors of the technical review on April 11, 2014. The information in the technical review was discussed in a systematic manner, facilitating subsequent creation of the guideline recommendations for or against each intervention. The strength of each recommendation was also rated as either strong or conditional.

Using the PICO format, which frames a clinical question by defining a specific patient population (P), intervention (I), comparator (C), and outcome(s), the guideline developers outlined a total of 9 questions (see Table 1 in the technical review [see the "Availability of Companion Documents" field]).

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Strength of Recommendations

Implications of strong and conditional (weak) guideline recommendations

- Strong recommendations
  - Patients: Most people in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.
  - Clinicians: Most patients should receive the recommended course of action. Adherence to this recommendation according to guidelines could be used as a quality criterion or a performance indicator.
  - Policy makers: The recommendation can be adapted as a policy in most situations.
- Conditional (weak) recommendations
  - Patients: The majority of people in this situation would want the suggested course of action, but many would not. Decision aids are useful in helping patients make decisions consistent with their values and preferences.
  - Clinicians: Examine a summary of the evidence to help patients make a decision that is consistent with their own values and preferences (shared decision making).
  - Policy makers: There is a need for substantial debate and involvement of stakeholders.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the use of pharmacological agents for the treatment of irritable bowel syndrome (IBS) in adults. The guideline was developed by the Clinical Practice and Quality Measures Committee (currently the Clinical Practice Guideline Committee) and approved by the AGA Governing Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate pharmacological management of irritable bowel syndrome (IBS) to improve patient symptoms and quality of life

Potential Harms

- Diarrhea leading to treatment discontinuation occurred in a small percentage of patients treated with linaclotide.
- Alosetron is only U.S. Food and Drug Administration (FDA) approved for use in women, and because of concerns about idiopathic, non-dose-dependent ischemic colitis (approximately 1 case/1000 patient-years), the drug was voluntarily withdrawn from the market and subsequently reintroduced only under a specific physician-based risk management program.
- Tricyclic antidepressants should be used with caution in patients at risk for prolongation of the QT interval.
- The most common adverse events reported with antispasmodics were dry mouth, dizziness, and blurred vision, but no serious adverse events were reported.

Qualifying Statements

Qualifying Statements

Irritable bowel syndrome (IBS) is complex and encompasses several subgroups, including patients with constipation-predominant symptoms (IBS-C) and those with diarrhea-predominant symptoms (IBS-D). Many of the pharmacotherapy recommendations outlined in the following text apply to only one of these subgroups.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S, American Gastroenterological Association. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014 Nov;147(5):1146-8. [4 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Nov

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Clinical Practice Guideline Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report. Dr Stollman has received research support from Furiex Pharmaceuticals for a study involving an investigational drug for irritable bowel syndrome with diarrhea (IBS-D).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Gastroenterology Journal Web site .

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814. E-mail: msiedler@gastro.org; telephone: (301) 941-2618.

Availability of Companion Documents

The following are available:

- American Gastroenterological Association Institute technical review on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014 Nov;147(5):1149-72. Electronic copies: Available from the Gastroenterology Journal Web site .
- The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013 Apr;11(4):329-32. Electronic copies: Available to subscribers from the Clinical Gastroenterology and Hepatology Web site .

Patient Resources

The following are available:

- Irritable bowel syndrome. Patient guide. Available from the American Gastroenterological Association Institute (AGAI) Web site .
- Comparing websites for patients: IBS. Patient guide. Available from the AGAI Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients

and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on May 26, 2015. The information was not verified by the guideline developer.

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